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EXCESS SAMPLE SIZE AND THE 'DELTA WOBBLE'
IN RANDOMIZED CONTROLLED TRIALS

Michael Adam Fischer

Yale University

1997

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Excess Sample Size and the 'Delta Wobble' in Randomized Controlled Trials

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Michael Adam Fischer

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ABSTRACT

EXCESS SAMPLE SIZE AND THE 'DELTA WOBBLE' IN RANDOMIZED CONTROLLED TRIALS.

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To determine the occurrence and consequences of excess sample sizes in large randomized controlled trials, we reviewed 158 randomized controlled trials, each containing more than 100 patients, published in *Lancet*, *Journal of the American Medical Association*, and *New England Journal of Medicine* during the three years 1990-1992.

Of 98 trials with statistically significant differences between control and experimental groups, the reported P values were less than 0.001 in 27 (28%) and less than 0.01 in an additional 35 (36%). Since sample sizes are usually calculated to provide P values of 0.05, the occurrence of values less than 0.01, and particularly below 0.001, suggests either that sample size was excessive or that the investigators found differences much larger than δ (the anticipated difference for "clinical importance"). The original anticipations were difficult to determine, however, because sample size calculations were not reported consistently: among the 158 trials, the details were presented completely in 78 (49%), but wholly omitted in 58 (37%). Of 54 trials that stated the value of δ and that found "statistical significance," 31 had P values below 0.01, but only 10 of these trials had observed differences that were at least 25% larger than δ ; in the remaining 21, the small P value was attained only by excess sample size. On the other hand, 15 trials found $P < 0.05$ and claimed statistical significance although the observed difference was at least 25% smaller than δ .

The problems of excessive sample size (and resources) probably arise from the customary Neyman-Pearson strategy, which tries to satisfy two (contradictory) statistical hypotheses, thereby making sample size much larger than what is needed for a single null hypothesis. The excessive sample size may then allow "statistical significance" to be found and emphasized for differences much smaller than what was originally anticipated.

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I. INTRODUCTION

“The value for which $P=.05$, or 1 in 20, ... is convenient ... as a limit in judging whether a deviation is to be considered significant or not.” ¹, p. 44

Sir Ronald Fisher originally made the above definition in 1925. Today the threshold of P below 0.05 remains the principal criterion for statistical significance, often representing the difference between research that changes current practice and research that does not. In many clinical trials, however, the authors report P values that are much smaller than 0.05. Very small P values can arise either because the difference in the event rates reported is much larger than originally anticipated or because the sample size was excessively large.

This research was aimed at documenting the frequency with which randomized controlled trials in major medical journals report very small P values, and to suggest possible reasons for the phenomenon. The research data were obtained by reviewing the sample size calculations and the subsequent results described in the published trials.

The remainder of this section contains a review of previous literature on sample size calculation in randomized controlled trials. Section II describes the methods used to assemble a group of randomized controlled trials for review and to abstract data from those articles. Section III presents the main results of the study, including the range of P values in the reviewed articles, the extent of reporting for sample size calculations, and the differences between the reported and the originally anticipated event rates. Section IV

discusses the implications of the results in Section III and shows some illustrative examples of calculations of sample size. Section V contains the conclusions.

A. Literature Review of Studies Reporting on Sample Size Calculation

Previous studies of the reporting of sample size calculation in randomized controlled trials have repeatedly shown that most authors do not report the details of their sample size calculations. In 1978 Ambroz et al. reviewed 172 randomized controlled trials and found that none of the publications reported a sample size calculation ². A 1982 review of 67 randomized controlled trials found that 12% of the articles reported the details of the sample size calculation and 3% provided partial information about the sample size calculation ³. In 1986, a survey of the breast cancer literature by Liberati et al. revealed that 20 (32%) of 63 articles had reported sample size calculations in the text ⁴. In follow-up phone calls, 13 more sets of authors provided the details of sample size calculation that had not been presented in the text ⁴. In a 1987 review, 5 (11%) of 45 articles reported sample size calculations ⁵. In 1990 Altman and Dore found some improvement in completeness of reporting: 31(39%) of 80 trials reported details of the sample size calculations and only 27(34%) of 80 articles made no mention of advance consideration of sample size ⁶.

Two large literature reviews in 1994 showed that reporting of sample size calculation methodology had become more widespread than in 1978 but was still far from universal. In a review of the obstetrics and gynecology literature from 1990 and 1991,

Schulz and co-authors found that only 50 (24%) of 206 articles reported sample size calculations ⁷. These authors also found considerable variation between journals in the extent of reporting of sample size calculation ⁷. Moher et al., in a sample of articles from 1975 to 1990, found that 33(32%) of 103 reported sample size calculation ⁸. The proportion of articles reporting sample size calculation had increased over time, from 0% in 1975 to 43% in 1990 ⁸.

B. Studies Arguing for Larger Sample Sizes

The attempt to determine the proper sample size for a randomized controlled trial can be seen as both a practical and an ethical concern:

A study with an overlarge sample may be deemed unethical through the unnecessary involvement of extra subjects and the correspondingly increased costs. ... On the other hand, a study with a sample that is too small will be unable to detect clinically important effects. Such a study may be scientifically useless, and hence unethical in its use of subjects and other resources. ^{9, p. 1336}

Over the last two decades, the predominant argument made in the medical literature has been for larger sample sizes.

The importance of large samples to avoid type II error, or false negative conclusions, in randomized trials was brought to prominence by Freiman et al. ¹⁰ in an influential article, nearly 20 years ago, that noted many trials reporting no difference between control and experimental groups were in fact not able to rule out differences as large as 25 or even 50 percent. Freiman et al. urged that much larger sample sizes would

be needed to state conclusively that there was no difference between control and experimental groups. In a recent article that revisited the issue originally raised by Freiman et al., Moher et al. found that many clinical trials reporting no difference still did not have samples large enough to exclude effects of 25 or 50 percent⁸.

On the other hand, during informal reviews of the literature, several readers had noted extremely small P values, suggesting that sample sizes were substantially larger than needed to achieve the boundary of 0.05. The current study was evoked by questions about the frequency and sources of the “too-large-sample” phenomenon.

II. METHODS:

A. *Assembling the Articles*

For this review, I chose randomized controlled trials published in *Lancet*, *New England Journal of Medicine*, and *Journal of the American Medical Association* during the three year period from 1990 through 1992, inclusive. This choice follows the method of two prior studies. In one of the most widely cited reviews of statistical methods in the medical literature, Freiman et al.¹⁰ examined articles from several journals, but more than one-half of the articles came from these three journals. In their later review of the same topics, Moher et al.⁸ also examined articles in those same three journals. With the

emphasis on large clinical trials, I restricted my search to articles with a sample size of at least 100 patients.

Table 1 summarizes the literature search and the criteria for exclusion of articles. Using the Medline computer program in the summer of 1994, I restricted the search to "*Clinical Trial*," "*Multicenter Study*," and "*Randomized Controlled Trial*." The search produced 1003 articles, which were reviewed to determine appropriateness for this study. I made certain simple exclusions by inspecting the abstracts cited by Medline, but other exclusions required review of the text of the articles. The search produced many articles, including letters (276), editorials (56), reviews (8), meta-analyses (9), and news summaries (16), all of which I excluded. The 238 articles that described trials containing fewer than 100 patients were also excluded, as well as 102 articles that were not randomized controlled trials, having been obtained via the headings "*Clinical Trial*," and "*Multicenter Study*". Additional exclusions were 84 trials whose primary outcome measure was not a rate or proportion, 21 trials that were designed to show equivalence (rather than efficacy) between control and experimental groups, 11 trials that were designed to demonstrate vaccine efficacy, eight trials that had multi-stage randomization schemes or other complexities that made them inappropriate for this analysis, and six that were follow-up cohort studies of patients from prior randomized controlled trials. Appendix A lists full citation information on the included articles.

Table 1: Details of literature search

	NEJM	Lancet	JAMA	Total
Articles Identified	396	490	117	1003
Excluded because:				
Letter to editor	82	190	4	276
N<100	84	131	23	238
Not rand. controlled trial	36	50	16	102
Not measuring event rate	38	30	26	84
Editorial	47	8	1	56
Trial for equivalence	14	6	1	21
“News”	1	2	13	16
Vaccine trials	4	7	0	11
Meta-analysis	2	1	6	9
Review article	1	6	1	8
Complex randomization	3	3	2	8
Follow-up studies	0	2	4	6
TOTAL EXCLUDED	312	436	97	845
TOTAL KEPT	84	54	20	158

After the exclusions cited in Table 1, the remaining 158 articles were each reviewed and suitably excerpted for descriptions of the sample size calculations. For trials that reported a statistically significant difference between experimental and control groups, the magnitudes of the main difference between groups, and the corresponding P value, were recorded. The remainder of this section describes the recorded components of the sample size calculation.

B. Introduction to Neyman-Pearson Equation

The most widely accepted method for calculating sample size is the Neyman-Pearson equation, shown below:

$$n \geq \frac{(Z_\alpha + Z_\beta)^2 \times [2 \times \pi_c \times (1 - \pi_c)]}{\delta^2} \quad (1)$$

In this equation, n represents the number of subjects that will be required in each of two groups. Z_α represents the Z-score that corresponds to the designated value of α , which is the risk of type I error that the authors are willing to accept. Z_β represents the Z-score that corresponds to the designated value of β , which is the risk of a type II error. π_c represents the estimated value for the event rate expected in the control group, and the quantity $[2 \times \pi_c \times (1 - \pi_c)]$ represents the variance of that rate. δ represents the anticipated difference that the authors hope to find between rates in the control and experimental groups.

The Neyman-Pearson sample size calculation requires two basic decisions: the first is defining the levels of significance that will be used as cutoff points for α and β ; and the second is estimating event rates. If both of these decisions are fully described, a reader can replicate the sample size calculation and, aware of statistical assumptions made in trial design, can understand the importance of the subsequently reported P value.

The level of significance for rejecting the null hypothesis is defined by the designation of α , typically 0.05 and traditionally two-tailed. It corresponds to a Gaussian Z_α value of 1.96. The α value of 0.05 implies a 5% risk of a type I error, in rejecting a true null hypothesis, so that the observed finding arises from chance alone. The risk of type II error, in rejecting a true alternate hypothesis of a large difference between groups, is defined by β , which can have various values, but is often designated at 0.10. β can be either one- or two-tailed. The assigned value of β is often stated implicitly as the power of the study, which is calculated as $1-\beta$, so that the most commonly assigned power for a study is 90%.

For the studies that provided a sample size calculation, I recorded whether the α or β designations were described, and also listed as one- or two-tailed. Presentation of the power of a study was considered equivalent to presenting the value of β .

The other important decision in sample size calculation is a prior estimation of event rate in the control group (π_c) and the change (δ), i.e. delta, that the authors believe

would represent a clinically significant finding. In Equation 1 the required components are the variance $[2\pi_c(1-\pi_c)]$ of the rate in the control group in the numerator and δ in the denominator. Many authors do not present both of these designations. When authors present only the δ that they hoped to find, it is helpful for reviewing the final outcome of the trial, but does not provide enough information for the reader to re-create the sample size calculation. Many authors do not cite the absolute difference which they hoped to find for δ , but instead describe θ , the desired proportional (or relative) change, which would usually be calculated as δ/π_c . The presentation of only θ gives some information about the authors' assumptions, but does not allow re-creation of the sample size calculation. The sample size calculation can be replicated only if authors provide their prior designation of π_c together with any citation of π_c (the anticipated rate in the experimental group), δ , or θ .

For the articles that provided sample size calculations, I recorded which of these features were reported.

III. RESULTS

A. *Range of P Values*

Of the 158 articles in this sample, 104 reported statistically significant differences between the control and experimental groups. Of those 104 articles, the six that did not use P values in discussing the results were not included in this section. Table 2 shows that among the 98 articles with statistically significant outcomes, 27 (28%) reported P values less than or equal to 0.001, 35 articles (36%) had P values that were between 0.01 and 0.001, and the remaining 36 articles reported P values between 0.05 and 0.01.

Given that $P < 0.05$ is the commonly accepted threshold for statistical significance, it seems surprising that over 25% of the articles reported P values 50 times smaller than the threshold value (i.e. ≤ 0.001). Two possible explanations could account for these extremely small P values: the observed difference (hereafter referred to as d_0) found to be statistically significant might have been much larger than the difference (δ) that the authors expected to find; alternatively, the number of patients in the trials might have been much larger than needed to achieve significance at the $P < 0.05$ level*. To assess the frequency of these explanations, the original sample size calculations must be examined to determine the event rates that were estimated when the trial was designed.

* Section III.C will point out a third explanation - altered variance - for small P values, and the example in Section IV.B.3 will expand on that explanation

Table 2: Range of P values in trials with statistically significant outcomes

P value	Number of articles(%)
$P \leq 0.001$	27 (28%)
$0.001 \leq P \leq 0.01$	35 (36%)
$0.01 \leq P \leq 0.05$	36 (37%)

B. Sample Size Calculations

1. Presentation of Sample Size Calculations

Table 3 summarizes the ways in which authors reported their sample size calculations. Of the 158 large, randomized controlled trials under analysis, 58 (37%) were reported with no description of how sample size was calculated and with no reference to a previously published calculation. Of 100 (63%) that provided at least some description of the calculation, 12 required reference to a prior publication to find some or all of the main components in the sample size calculation. The cited 100 articles were stratified into the several groups shown in Table 3. The first column shows that 78 reports provided prior designations of event rates. The remaining 22 articles provided less detailed descriptions that would limit a reader's ability to fully understand the assumptions that went into the sample size calculation.

The rows of Table 3 show the extent to which authors noted their prior designations of α and β . For the sake of simplicity this table does not include whether authors indicated if their designations of α and β were one- or two-tailed. Almost half of the authors who presented a value of α classified it as one- or two-tailed (42/87), while very few authors noted whether their values of β were one- or two-tailed (6/91). The first row shows that 83 articles (53% of the total sample) presented both α and β designations. Only four authors (3%) presented only α values (2nd row) and eight (5%) reported only β values (3rd row). The fourth row of Table 3 shows that in addition to the 58 articles that

Table 3: Elements reported for sample size calculation

	Designation of π_c and δ described *	Designation of δ described, but π_c not described	Designation of θ described, but neither π_c nor δ described	No event rate designations described	TOTAL
Designations of α and β described	67	5	9	2	83
Designation of α alone described	2	1	0	1	4
Designation of β alone described	4	1	3	0	8
Neither α nor β designation described	5	0	0	58	63
TOTAL	78	7	12	61	158

* π_c or θ were acceptable substitutes for δ

did not describe any sample size calculation, five others (with some description) did not include their designations of either α or β .

The columns of Table 3 show the frequency with which authors reported their prior estimations of outcome rates in the control and experimental groups. As noted earlier, proper interpretation of results requires knowledge of π_c and of δ , although the value of δ could be calculated by subtraction if π_c and π_e are described, or by appropriate multiplication if π_c (or π_e) and θ are described. The first column shows that 78 articles (49% of the total sample) either provided both π_c and δ , or provided π_c and enough information for δ to be easily calculated. Smaller numbers of articles presented either δ alone (2nd column, 7/158, 4%) or θ alone (3rd column, 12/158, 8%). No articles in the sample reported π_c alone without some indication of the desired change, but the fourth column shows that, beyond the 58 articles with no information on the sample size calculation, only three articles gave no indication of the estimated event rates or desired differences.

2. *Completeness of Reporting for Sample Size Calculation*

As noted earlier, a complete description of the sample size calculation would allow understanding of the methods used by the investigators. The 67 trials in the upper left-hand corner of Table 3 provided complete or near-complete descriptions of sample size calculations, limited only by inconsistent reporting of whether α and β were one- or two-

tailed (four articles reported this information for both α and β). Similarly, for the 11 articles in the rest of the first column of Table 3, values of π_c and δ are described (although α and β are not both reported) so that a reader could appreciate the connotation of the P values reported by the authors.

For the 19 articles in the middle two columns of Table 3, the reader would be hard-pressed to understand the sample size calculation. A determined reader could make multiple guesses at the designation of π_c , perhaps getting a sense of the prior estimates but the process would be quite laborious. For the 61 articles in the right-hand column of Table 3, there is no way for a reader to understand the sample size calculation, especially for the 58 articles that provided no details at all.

In summary, only 4 of the 158 articles (3%) reported all of the information needed to understand the sample size calculation, but an additional 63 articles (40%) offered almost complete information. Eleven articles (7%) provided incomplete information but described the critical rates that would allow the reader to evaluate the outcome of the trial. Nineteen additional articles (12%) offered information that might allow for a general sense of the sample size calculation, but was too limited for full evaluation of the results. Sixty-one articles (39%) did not provide information that would allow any realistic attempt at understanding the sample size calculation. There was no correlation between the actual sample sizes in the trials and the extent of reporting of the sample size calculations.

Overall, 78 of the articles (49%) provided enough information for readers to understand the important components of the sample size calculation.

For the 78 articles which presented their prior designations of event rates, if significant differences were found, readers could evaluate the magnitude of the P values reported. Table 4 shows that of the 158 total articles reviewed, 54 both described π_c and δ and reported statistically significant outcomes. The following sections will compare prior estimates and reported results for these 54 articles.

C. *Example of P Value Calculation*

The P value used to determine statistical significance is based on a Z-score derived from the following equation:

$$Z = \frac{d_0}{SED} = \frac{p_c - p_e}{\sqrt{\bar{p}(1 - \bar{p}) \left[\frac{1}{n_c} + \frac{1}{n_e} \right]}} \quad (2)$$

In this equation, the numerator, d_0 , is equal to p_c (the outcome rate in the control group) minus p_e (the outcome rate in the experimental group). The denominator for this calculation is the standard error of the difference between groups (SED). For its calculation, \bar{p} is the average outcome rate (i.e. the average of p_c and p_e), n_c is the number of patients in the control group, and n_e is the number of patients in the experimental group.

Table 4: Criteria for inclusion of articles in analysis of δ versus d_0

	Articles reporting a statistically significant d_0 with a P value		TOTAL
	Yes	No	
Articles that reported both π_c and δ	54	24	78
Articles that did not report both π_c and δ	44	36	80
TOTAL	98	60	158

Higher Z-scores correspond to lower P values; for example a Z-score of 1.645 corresponds to a two-tailed P value of 0.10 while a Z-score of 1.96 yields the familiar two-tailed P value of 0.05. Equation 2 shows that a Z-score could increase in three ways. An increase in d_0 would enlarge the numerator; alternatively, either an increase in n_c or n_e or a decrease in the variance would reduce the denominator. The next section will compare the range of observed d_0 values and the anticipated δ values in this group of articles.

D. Differences Between d_0 and δ

Table 5 shows that, of the 54 articles which reported both prior designations of event rates and statistically significant outcomes, the observed value of d_0 was greater than or equal to the prior assignment of δ in 29 cases, but 25 articles reported statistical significance for a d_0 that was smaller than the prior designation of δ . We have named this latter phenomenon “ δ (delta) wobble” and will explain the term more completely later in the Discussion. In four extreme instances, the observed d_0 was at least 50% smaller than the anticipated δ . As an example of “ δ wobble,” in one of the articles¹¹ included in the second-to-last row of Table 5, a δ value of 0.30 was designated for the purposes of sample size calculation, but a statistically significant d_0 of 0.152 was presented in the results section. Thus for this article d_0 was smaller than δ by 49% [i.e. $(d_0 - \delta)/\delta = (0.152 - 0.30)/0.30 = -0.49$]. At the other extreme, in one of the articles¹² included in the first row of Table 5, a δ of 0.20 was

**Table 5: Frequency of values for the proportionate difference $(d_0 - \delta)/\delta$
(Negative percentage for $d_0 < \delta$, positive percentage for $d_0 > \delta$)**

Percent difference between d_0 and δ	Number of articles
>50%	10
25% to 50%	6
0% to 25%	12
0%	1
-25% to 0%	10
-50% to -25%	11
<-50%	4

designated for sample size calculation, but a d_0 of 0.37 was presented in the results section. For this article d_0 was greater than δ by 85% $[(0.37-0.20)/0.20 = 0.85]$.

The final row of Table 5 show that of the 25 articles with “ δ wobble,” i.e. a d_0 value less than the prior designation of δ , four presented a statistically significant d_0 that was less than half as large as δ (first row). An additional 11 articles presented d_0 values that were smaller than δ by a proportionate increment between one-quarter and one-half (second-to-last row). Seven of the 25 articles with “ δ wobble” presented a statistically significant d_0 value that was less than δ by an absolute increment of more than 0.10.

Table 6 shows the relationship of discrepancies between d_0 and δ to the magnitude of P values reported. As noted previously, increased d_0 values could cause very small P values. The first two rows of Table 6 show that of the 31 trials which reported δ and had P values less than or equal to 0.01, 10 had d_0 values more than 25% larger than the prior designation of δ , but 12 of the 31 trials with $P \leq 0.01$ had d_0 values that were smaller than the prior designation of δ . Table 6 demonstrates that the very small P values are not restricted to trials reporting d_0 much larger than δ . Indeed, the final three rows show that even some of the trials that commit “ δ wobble” report very small P values.

Table 6: Frequency of values for the proportionate difference $(d_0 - \delta)/\delta$, categorized by magnitude of reported P-value in statistically significant trials. Last row contains those articles which did not report original designation of δ .

Percent difference between d_0 and δ	$P \leq 0.001$	$0.001 \leq P \leq 0.01$	$0.01 \leq P \leq 0.05$	Total
>50%	4	2	4	10
25% to 50%	3	1	2	6
0% to 25%	2	6	4	12
0%	1	0	0	1
-25% to 0%	0	6	4	10
-50% to -25%	1	4	6	11
<-50%	0	1	3	4
Total reporting δ	11	20	23	54
No δ described	16	15	13	44
Grand Total	27	35	36	98

IV. DISCUSSION

A. *Reporting of Sample Size Calculations*

The current finding, that 43% (67/158) of a group of published randomized controlled trials presented full details of sample size calculations, was only slightly higher than the 39% found in a 1990 review ⁶ and was identical to the rate noted in an analogous review published in 1994. ⁸ The finding that 39% (58/158) of articles reported no details of sample size calculation was also similar to the rate noted in a 1990 review ⁶.

Although the details of sample size calculation are now reported more often than noted in the first such reviews almost 20 years ago ², reporting is still far from complete. In a 1994 review, Moher et al. suggested:

that authors should report sample size calculations and that the following information should be contained in all published reports of RCTs: (1) The primary dependent measure(s) should be clearly identified. (2) A clinically important treatment effect should be specified. (3) The treatment effect should be clearly indicated as being an absolute or a relative difference. (4) The statistical test, directionality, α level, and statistical power used to estimate sample size should be reported. ^{8, p. 124}

This suggestion was re-iterated in an article later in 1994 by The Standards of Reporting Trials Group, an international committee established to address reporting of randomized controlled trials ¹³. In light of the consequences that are about to be discussed, editors might follow the recommendations of Moher et al. and become more

demanding in asking authors to report their pre-trial assumptions when sample size was calculated.

B. Very Small P Values

As noted in Table 2, more than 25% of the trials with statistically significant results reported P values that were ≤ 0.001 . As shown in Equation 2, these excessively small P values could have come from unexpectedly large values of d_0 , but Table 6 shows that only 10 (32%) of the 31 articles with $P \leq 0.01$ found d_0 to be substantially larger than δ . The remainder of this section will show, however, that even for those 10 articles, the large d_0 values were not likely to have caused the excessively small P values.

1. An Example of an Article with d_0 Much Larger Than δ

In one article where δ was designated as 0.20 but d_0 was found to be 0.37, this distinction was reported as having a $P < 0.001$ ¹². The Z-score for this result can be calculated using Equation 2. In the article cited, p_c was 0.77, p_e was 0.40, n_c was 104 and n_e was 95¹². \bar{p} can be approximated as the weighted average of 0.77 and 0.40, which yields 0.593*. The Z-score is thus:

* This value is calculated as an average weighted by the number of subjects in each group:

$$\bar{p} = \frac{n_c p_c + n_e p_e}{n_c + n_e} = \frac{(104 \times 0.77) + (95 \times 0.40)}{104 + 95} = 0.593$$

$$Z = \frac{0.77 - 0.40}{\sqrt{0.593(1 - 0.593) \left[\frac{1}{104} + \frac{1}{95} \right]}} = 5.31 \quad (3)$$

Since a Z-score of 3.80 corresponds to a P value of 1×10^{-4} , this finding would not only result in $P < 0.001$, but would yield an infinitesimally small P value in the range of 1.0×10^{-7} ^{14, p. 31}.

2. *Effect of Discrepancy Between d_0 and δ on P Values*

If the d_0 in the above example had been the expected 0.20 instead of 0.37, i.e., if p_c was 0.60, the Z-score would be calculated as follows:

$$Z = \frac{0.60 - 0.40}{\sqrt{0.505(1 - 0.505) \left[\frac{1}{104} + \frac{1}{95} \right]}} = 2.82 \quad (4)$$

The corresponding P value would be less than 0.005 ^{15, p. 281}. Although much larger than the previous result for P, this value is still 10 times smaller than the boundary of 0.05 for achieving statistical significance.

3. *Effect of Discrepancy Between p_c and π_c on P Values*

In the cited article, however, not only was d_0 much larger than δ , but the observed event rates themselves were considerably larger than the values assigned prior to the study. The authors had previously estimated rates of 0.25 for the control group and 0.05

for the experimental group ¹². If these outcome rates had actually been found, the Z-score calculation would have shown:

$$Z = \frac{0.25 - 0.05}{\sqrt{0.155(1 - 0.155) \left[\frac{1}{104} + \frac{1}{95} \right]}} = 3.89, \quad (5)$$

which corresponds to a P value of 1×10^{-4} ^{14, p. 31}.

In this example the discrepancy between the observed and estimated event rates affected the variance term in the denominator. The closer \bar{p} is to 0.50, the larger the variance will be and the smaller the Z-score will be. The discrepancy between predicted and reported rates in this example moved \bar{p} very close to 0.50, but the P value was still reported as statistically significant by a wide margin. The more striking point, however, is that the Z-score calculated in Equation 5 represents the clinical outcome expected by the authors, but the corresponding P value is extremely small. If the very small P value is due neither to large d_0 values nor to discrepancies between p_c and π_c , the only remaining cause for the small P values is excessively large sample sizes.

C. *The Phenomenon of “ δ Wobble”*

In addition to showing that increased d_0 values seldom cause very small P values, Table 5 and Table 6 reveal an additional phenomenon. As noted in Section III.D, 25 of the 54 articles in Table 5 reported d_0 values smaller than δ ; indeed 15 of the “statistically significant” d_0 values were at least 25% smaller than δ . If the δ value entered into the

Neyman-Pearson equation represents the minimum boundary to be regarded as clinically significant, the frequent citation of “significance” for d_0 values much smaller than the pre-assigned δ calls into question the initial design of the trial. The remainder of this section will show a hypothetical sample size calculation to demonstrate that the Neyman-Pearson equation converts δ into a “wobbly” parameter. The calculated sample sizes will allow values of d_0 much smaller than δ to be declared statistically significant.

The values in the example below are chosen arbitrarily, but the results will hold for any set of values if readers want to replicate the exercise. The Neyman-Pearson calculation shown in Equation 1 in Section II.B is the standard method used for calculating sample sizes. The elements of the calculation were described in Section II.B and will not be repeated here.

1. Calculation of the Sample Size

For this example, I will assume that the mortality rate of 0.20 with current therapy for disease X is to be tested against a new treatment that is expected to reduce the mortality rate to 0.10. Following convention, the researchers designate an α value of 0.05 (two-tailed) and a β value of 0.10 (one-tailed) for the purposes of sample size calculation. The sample size calculated using the Neyman-Pearson equation will be as follows:

$$n \geq \frac{(1.96 + 1.282)^2 \times [2 \times 0.2 \times (1 - 0.2)]}{0.10^2} = 336 \quad (6)$$

The researchers therefore recruit a total of 672 patients to their study, 336 to receive current therapy and 336 to receive experimental treatment. With this backdrop, I will now consider possible outcomes.

2. *Scenario 1: d_0 Equal to δ*

In the first scenario, the researchers find exactly what they had expected. Mortality in the control group is 67/336, or 0.199, while mortality in the experimental group is 34/336, or 0.101. To test the statistical significance of these findings, the Z score is calculated with Equation 2 to show:

$$Z = \frac{0.199 - 0.101}{\sqrt{0.15(1 - 0.15) \left[\frac{1}{336} + \frac{1}{336} \right]}} = 3.56 \quad (7)$$

The corresponding two-tailed P value for this result is $0.0002^{15, p. 280}$, which is much smaller than the anticipated $P=0.05$, although the d_0 found by the researchers almost exactly equals the prior designation of δ .

3. *Scenario 2: d_0 smaller than δ , but is Statistically Significant*

In the second scenario, mortality in the control group is again 67/336, or 0.199, but mortality in the experimental group is 47/336, or 0.140. This d_0 of 0.059 is much smaller than what was hoped, but calculation of a Z score reveals:

$$Z = \frac{0.199 - 0.140}{\sqrt{0.170(1 - 0.170) \left[\frac{1}{336} + \frac{1}{336} \right]}} = 2.04 \quad (8)$$

This corresponds to a P value of 0.0414^{15, p. 280}. Armed with this result, the investigators can now present this d_0 of 0.059 as statistically significant, although it is almost half of the δ value of 0.10 which they designated as a difference worth finding before the trial began.

4. Scenario 3: d_0 Smaller than δ , but not Statistically Significant

In a third scenario, control group mortality remains at 67/336 (0.199), but one additional experimental group patient dies, so that experimental group mortality is 48/336, or 0.143. The d_0 of 0.056 is again smaller than the prior designation of δ . Calculation of the Z-score shows:

$$Z = \frac{0.199 - 0.143}{\sqrt{0.171(1 - 0.171) \left[\frac{1}{336} + \frac{1}{336} \right]}} = 1.93 \quad (9)$$

This corresponds to a P value that is slightly greater than 0.05^{15, p. 280}, so that the investigators cannot claim the result is significantly different from zero. Persevering, the researchers recall that the Z_β term in the sample size calculation was 1.282, corresponding to a one-tailed β of 0.10. A Z-score for the alternate hypothesis can be calculated using the following formula:

$$Z_A = \frac{\delta - d_0}{SED} \quad (10)$$

This is almost the same Z-score formula shown in Equation 2, but differing in the use of the quantity $\delta - d_0$ in the numerator*, and it results in the following calculation:

$$Z_A = \frac{0.10 - 0.056}{\sqrt{0.171(1 - 0.171)\left[\frac{1}{336} + \frac{1}{336}\right]}} = 1.51 \quad (11)$$

Since this value is greater than the threshold value of 1.282 used in the sample size calculation, the investigators can reject the alternate hypothesis of a large difference between groups. The investigators can now claim they have proven that there is no important difference between the two treatments, as their results excluded a difference of 0.10.

5. *A Zone of Double Significance*

A particularly interesting result arises, however, if we return to the scenario in Section IV.C.3, and to the Z-score calculated in Equation 8. If, for that same result, the researchers had calculated a Z_A for the alternative hypothesis:

$$Z_A = \frac{0.10 - 0.059}{\sqrt{0.170(1 - 0.170)\left[\frac{1}{336} + \frac{1}{336}\right]}} = 1.41 \quad (12)$$

* The SED for the alternate hypothesis is properly calculated as follows:

$$SED_A = \sqrt{\frac{p_c q_c}{n_c} + \frac{p_e q_e}{n_e}}.$$

In this example, both the above calculation and the calculation shown in the denominator of Equation 11 produce a value of 0.029. The standard calculation of SED will be used for the remaining examples.

This result is greater than the prior Z_β value of 1.282, and the investigators can declare that they have proven that there is no important difference between groups, as this result excludes a difference of 0.10. For this result, therefore, the investigators have achieved double statistical significance. The difference between groups is both statistically significantly greater than zero (Equation 8) and is also statistically significantly smaller than the difference initially defined as clinically significant (Equation 12).

6. *Neyman-Pearson Equation Shifts Threshold for Statistical Significance*

Although the investigators stated initially that a difference of 0.10 between treatments represented the boundary for clinical importance, the sample size calculated with the Neyman-Pearson equation would in fact allow them to declare statistical significance for a d_0 as small as 0.059, or any larger value. At that same level of d_0 , and at any smaller value, the investigators could declare that their result was statistically significantly smaller than 0.10. The crucial observation here is that when sample size is calculated with the Neyman-Pearson equation for this example, the investigators will find a statistically significant result no matter what value emerges for d_0 . The particular values shown in Section IV.C.5 will even achieve double significance; thus, the threshold for significance is no longer the clinical threshold that was used in trial design. In addition, when the final result does equal the threshold defined as clinically significant for trial design, the P value is orders of magnitude smaller than the 0.05 value that conventionally determines statistical significance.

D. *Calculation of Implicit Thresholds*

The example in the preceding section demonstrated some of the consequences of using a sample size generated by the Neyman-Pearson calculation. In this section I will show how those consequences arise. The crux of this argument is that the Neyman-Pearson calculation uses both Z_α and Z_β , thereby incorporating both null and alternate hypotheses in one formula. In the analysis of results, however, these hypotheses are evaluated separately, each with an individual calculation.

If one calculated a sample size considering only the possibility of type I error, the sample size calculation would be as follows:

$$n \geq \frac{(Z_\alpha)^2 \times [2 \times \pi \times (1 - \pi)]}{\delta^2} \quad (13)$$

This differs from the Neyman-Pearson calculation in that Z_β is not included. Conversely, if one calculated a sample size with concern for type II error only, the following equation would be used:

$$n \geq \frac{(Z_\beta)^2 \times [2 \times \pi \times (1 - \pi)]}{(\delta - d_0)^2} \quad (14)$$

In this case, Z_α has been excluded from the numerator. Additionally, the denominator term $(\delta - d_0)$ reflects the increment at which a difference of δ will be ruled out at the Z_β level of significance.

Combining the previous two equations with the results of the example from the previous section, I will now demonstrate that the thresholds for statistical significance are not those demarcated in the Neyman-Pearson equation. In Equation 6, the calculated sample size was 336 patients per group. With this sample size, consider Equation 13. Inserting 336 for N, 1.96 for Z_{α} , and keeping the same term in the denominator, the result is as follows:

$$336 = \frac{(1.96)^2 \times [2 \times 0.2 \times (1 - 0.2)]}{\delta^2} \quad (15)$$

Rearranging equation 15 to solve for δ produces:

$$\delta = \sqrt{\frac{(1.96)^2 \times [2 \times 0.2 \times (1 - 0.2)]}{336}} = 0.060 \quad (16)$$

The implication of the above calculation is that although a δ value of 0.10 was designated when the Neyman-Pearson equation was used to calculate sample size, the result in fact represents an implicit δ designation of 0.060. In other words, although the study design designates a difference of 0.10 as clinically important, differences as small as 0.060 will be found to be statistically significant. This result explains both the findings summarized in section III.D and the outcome of the example trial presented in section IV.C.

The same process can be utilized for the calculation shown in Equation 14. Again combining that equation with the result of Equation 6, but omitting the intermediate steps, the final result will be as follows:

$$\delta - d_0 = \sqrt{\frac{(1.282)^2 \times [2 \times 0.2 \times (1 - 0.2)]}{336}} = 0.040 \quad (17)$$

Since the prior designation of δ in this example was 0.10, this result shows that for any d_0 value of 0.060 or smaller, the Z_A value for the alternate hypothesis will be greater than 1.282 and the alternate hypothesis of a large difference between control and experimental groups will be rejected.

The results of Equations 16 and 17 converge around a d_0 value of 0.060. The preceding paragraphs show that for the sample size determined with the Neyman-Pearson calculation in Equation 6, any value larger than 0.060 will be statistically significantly greater than 0, while any value smaller than 0.060 will be statistically significantly smaller than 0.10. In fact, since the SED is used for Z-score calculation (see Equation 2) and the variance of the control group rate is used in the standard form of the Neyman-Pearson formula (see Equation 1), the actual numbers in Section IV.C stretch further, so that values somewhat smaller than 0.060 will be statistically significantly greater than 0, and some of these values will also be statistically significantly smaller than 0.10. In practical terms, then, the Neyman-Pearson sample size calculation has guaranteed a statistically significant result in one direction or the other, and has even created a zone of double significance. The value 0.060 has now become the threshold at which the therapy being studied will be declared effective or ineffective, although this value is barely half of the value originally designated by the investigators. This result is not particular to the numbers chosen for this example, and will be found with any other set of values that are chosen for the illustration.

V. CONCLUSION

This paper has attempted to show consequences of excess sample size in large randomized controlled trials. Since a landmark paper by Freiman et al. almost 20 years ago, most discussion of sample sizes has focused on the need for larger samples. The results of the present study, however, suggest that enlargement of sample sizes, and in particular the use of the Neyman-Pearson equation to calculate these large samples, may have two important unintended consequences.

The first consequence is that with the large sample sizes generated by the Neyman-Pearson equation, many results will produce extremely small P values, despite the general acceptance of 0.05 as the threshold for a statistically significant finding. As noted in the introduction, an overly large sample generates excess cost and requires an excessive number of patients. As research funding dwindles, the excessive costs of oversized trials represent a substantial overuse of resources.

The second consequence of sample sizes calculated with the Neyman-Pearson equation is that the quantitative threshold for an impressive difference is reduced to almost half of the initial level. Thus, whatever δ investigators designate at the outset of the trial, the d_0 that can be declared statistically significant will be considerably smaller than the original value of δ ; we have named this phenomenon “ δ wobble.” The “wobbliness” of the boundary for clinical significance defined for sample size calculation undermines the clinical judgment used in originally defining δ .

The problems of excessively small P values and “ δ wobble” suggest that the Neyman-Pearson strategy of sample size calculation requires serious reevaluation. It is beyond the scope of this paper to suggest alternative methods for sample size calculation. Until such methods are developed, however, editors can address the problem of “ δ wobble” by requiring investigators to state both δ and d_0 , and to justify reporting of statistically significant d_0 values which are smaller than the δ initially designated as clinically significant.

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APPENDIX A: ARTICLES REVIEWED

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